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Rejoinder to “A note on testing and estimation in marker-set association study using semiparametric quantile regression kernel machine”

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The authors replied as follows:

We applaud Zhan and Wu (2017) for presenting an alternative strategy for p-value calculation of quantile regression kernel machine (QRKM) (Kong et al., 2016). In the QRKM paper, we considered the problem of estimation and testing for association between a phenotype of interest and a marker-set under the QRKM framework, where the response values may contain outliers or have a skewed or heavy-tailed distribution. Zhan and Wu (2017) considered the testing problem in our paper and developed a fast QRKM (FQRKM) test based on a fast permutation method, which significantly improves the computational speed.

The testing procedure in QRKM is not fast mainly due to the heavy computation cost to calculate the null distribution of the score-type statistic. To mimic the null distribution, we need to fit the full model once and obtain the residuals, where the bootstrap tuning takes a significant amount of time. We then need to fit the null model N times, and calculate the permuted statistics for N times, where N is the number of permutations needed. This step also takes some time to run. Zhan and Wu (2017) proposed a neat idea to overcome the computational barrier. Instead of using explicit permutations to obtain the null distribution of the QRKM statistic, they considered a modified version, denoted by FQRKM statistic, which has a close connection with fast permutation testing strategies (Josse et al., 2008) developed for RV-type statistic. The main advantage of using the FQRKM statistic is that the null permutation distribution can be approximated by a simpler and known distribution. They adopted the Pearson type III approximation, where fast and analytical p-value calculation is allowed.

Zhan and Wu (2017) have shown that FQRKM test has similar performance as QRKM test regarding type I error and power using simulations. The minor issue of the FQRKM test is

that the type I error is slightly inflated in lower or upper quantile when the sample size is small. We suspect that the Pearson type III approximation may not be very accurate under these scenarios, which causes the slightly inflation of the type I error. We have further applied the FQRKM test to the Vitamin Intervention for Stroke Prevention (VISP) Trial studied in Kong et al. (2016). We perform the same analysis on the nine candidate genes with 1587 subjects, considering the Homocysteine level at the quantiles of 0.1, 0.5 and 0.8 as our response variable, and using FQRKM test instead of our original QRKM test. The total computational time of FQRKM test is less than half an hour for all genes and all quantile levels, which is significantly faster than our original QRKM test, where we had to use separate node for each gene and each quantile. The test results are summarized in Table 1. From the results, we can see that the FQRKM test yields similar p-values as the QRKM test for each gene and each quantile level. We also find the gene *CBS* is significant at the quantiles 0.5 and 0.8, and the gene *TCN1* is significant at the quantile 0.8 after Bonferroni correction (i.e., $0.05/(9 \times 3) = 0.00185$). The conclusions based on FQRKM are the same as our original QRKM test. The simulation results in Zhan and Wu (2017), as well as the VISP data analysis, show that FQRKM test has very similar performance as the QRKM test. Since FQRKM test is significantly faster than QRKM test, we recommend the readers to use the FQRKM test instead if they want to test for association between the genetic covariates and the response under the QRKM framework when the sample size is not small. For the estimation under the QRKM, the readers may still use the procedure proposed in Kong et al. (2016).

Finally, we want to bring the readers' attention to two interesting problems for future research. The first problem is related to the tuning method in our QRKM paper. In our estimation procedure, we used the bootstrap tuning, which has high computational cost especially when sample size and dimension of the covariates are large. We adopted the bootstrap tuning mainly for two reasons. First, it is more stable. We had tried other tuning methods such as Schwarz information criterion (Schwarz, 1978), cross validation and generalized approximate cross validation (Yuan, 2006), although these tuning methods worked well in some Monte Carlo runs, they failed in other cases, ending up with very bad estimates. There is a tradeoff between computation speed and stability of the solution. Second, by using bootstrap tuning, we can get standard error estimates for $\hat{\beta}$ and $\hat{\beta}_0$ as a byproduct; however, the standard error estimates can also be obtained if the asymptotic distribution of the estimates can be derived. Studying the asymptotic theories under the QRKM would be an interesting research topic. The second problem in QRKM/FQRKM is related to the multiple testing procedure in the VISP real data analysis. Currently, we use the Bonferroni correction, which may be very conservative because the estimates across different quantiles are in fact correlated. It is worth further investigation on multiple testing procedures across different quantiles.

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Table 1

Results from the VISIP trial. Columns 2–4 display the p-values of QRKM test for the 9 genes on different quantiles 0.1, 0.5, 0.8. Columns 5–7 display the p-values of FQRKM test for the 9 genes on different quantiles 0.1, 0.5, 0.8.

Gene name	QRKM, $\tau = 0.1$	QRKM, $\tau = 0.5$	QRKM, $\tau = 0.8$	FQRKM, $\tau = 0.1$	FQRKM, $\tau = 0.5$	FQRKM, $\tau = 0.8$
<i>BHMT</i>	0.072	0.108	0.263	0.052	0.153	0.332
<i>BHMT2</i>	0.222	0.371	0.748	0.218	0.463	0.734
<i>CBS</i>	0.013	0.0004	0.0004	0.010	0.0002	0.0008
<i>CTH</i>	0.559	0.432	0.820	0.404	0.384	1.000
<i>MTHFR</i>	0.745	0.478	0.429	0.913	0.505	0.611
<i>MTR</i>	0.785	0.864	0.572	0.718	0.760	0.763
<i>MTRR</i>	0.020	0.070	0.860	0.018	0.062	0.999
<i>TCN1</i>	0.808	0.218	0.0006	0.841	0.195	0.0009
<i>TCN2</i>	0.455	0.622	0.835	0.398	0.703	0.937